DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Harris Rotman, Director
Global Regulatory Affairs
Shire Development, Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

RE: NDA #022037
Intuniv™ (guanfacine) extended-release tablets
MACMIS #18583

Dear Mr. Rotman:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed a DTC Patient Starter Kit (INT-00225), which includes a Parents' Guide (INT-00394), inPROGRESS Guide (INT-00219), Titration Guide (INT-00224), and a Free ADHD Support Guide (INT-00396), and a DTC In-Office Waiting Room Brochure (INT-00342) and DTC In-Office Waiting Room Brochure Custom Holder (INT-00343) for Intuniv™ (guanfacine) extended-release tablets submitted by Shire Development, Inc. (Shire) under cover of Form FDA-2253. These promotional materials are false or misleading because they present unsubstantiated effectiveness claims, omit and minimize important risk information associated with Intuniv and present unsubstantiated superiority claims. Therefore, the promotional materials misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (xviii) & (e)(7)(viii).

Background

The INDICATION AND USAGE section of the FDA-approved product labeling (PI) for Intuniv states the following (in pertinent part):

> INTUNIV™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). . . .
>
> A diagnosis of ADHD implies the presence of hyperactive-impulsive and/or inattentive symptoms that cause impairment and were present before the age of 7 years. . . . For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids task requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting

> answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met. . . .
>
> .
>
> Need for Comprehensive Treatment Program
>
> INTUNIV™ is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, and social) for patients with this syndrome. . . .

Intuniv is contraindicated in patients with a history of hypersensitivity to Intuniv, its inactive ingredients, or other products containing guanfacine (e.g., Tenex®). The PI also contains Warnings and Precautions regarding the risks of hypotension, bradycardia, and syncope, sedation and somnolence, and concomitant use with other guanfacine-containing products (e.g., Tenex®). The most common adverse reactions associated with the use of Intuniv are somnolence, sedation, abdominal pain, dizziness, hypotension/decreased blood pressure, dry mouth, and constipation.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience. The Waiting Room Brochure, Brochure Holder, and Parents' Guide present an image of a child dressed in a monster suit to represent a patient with ADHD. This image is presented in conjunction with claims such as the following (emphasis in original):

- "**Does your child's ADHD treatment get to what matters?** (Brochure Holder)

  Reveal the kid within
  A difference the whole family can see" (Brochure Holder, Waiting Room Brochure cover)

- "**The symptoms of ADHD (attention-deficit/hyperactivity disorder) can hide who your child really is and disrupt family life. If you can separate the kid from the symptoms, you and your family may see more of the great kid inside. That's where INTUNIV comes in.**
  Revealing a difference the whole family can see" (Parents' Guide, page 2)

The promotional materials also include the claim, "imagine the moments ahead," as a tagline throughout the pieces.

Furthermore, page 4 of the inPROGRESS Guide presents "**Issues**" associated with ADHD, including the following (emphasis in original):

- "**Bedtime blowups**"
- "**Toothbrushing tantrums**"
- "**Homework hassles**"
- "**Dinnertime defiance**"

- "**Sibling struggles**"
- "**Excessive energy"**
- "**Mall meltdowns**"

This presentation is followed by a presentation of "**Progress**" on page 6, which includes the following (emphasis in original):

- "**Manageable mornings**"
- "**Assignments accomplished**"
- "**Drama-free dinnertime**"

Page 2 of the Waiting Room Brochure contains a graphic of two children fighting over a stuffed toy as their parents look on disapprovingly. This graphic is presented in conjunction with the following claims (bolded emphasis in original; underlined emphasis added):

- "When you think about ADHD (attention-deficit/hyperactivity disorder) chances are you think about struggles in school, lack of focus, or restlessness. But there can be more to the story.

  ADHD symptoms can also include temper outbursts, arguing with adults, and deliberately annoying others. When you live with these symptoms every day, you know they're not only tough for your child. They can disrupt family life." (page 2)

- "**Tell your child's doctor about <u>temper outbursts</u>, fidgeting, and <u>irritability</u> You may not think of these as symptoms of ADHD**" (page 3)

This presentation is followed by a graphic of the same children on page 4 playing a board game together nicely as their parents smile at them, in conjunction with the claims, "**Ask the doctor if once-a-day INTUNIV could make a difference for your child**" and "**Parents and teachers reported that INTUNIV improved symptoms**" (emphasis in original).

Page 5 of the Waiting Room Brochure also presents claims such as the following (bolded emphasis in original; underlined emphasis added):

- "**INTUNIV has been studied across a range of symptoms, including**
  - Not being able to focus
  - Moments of distraction
  - <u>Arguing with adults</u>
  - <u>Irritability</u>
  - <u>Temper outbursts</u>
  - <u>Deliberately annoying others</u>
  - Impulsiveness or overexcitement"

The Parents' Guide includes similar claims and further references a "**checklist from the Conners' Parent and Teacher Rating Scales to assess a range of your child's ADHD symptoms**. . . " before listing symptoms such as those underlined above (emphasis in original).

The overall impression conveyed by the above claims and presentations is that treatment with Intuniv will improve **individual** behavioral problems in children with ADHD that "the whole family can see." FDA is not aware of substantial evidence or substantial clinical experience to support this implication. According to the CLINICAL STUDIES section of Intuniv's PI, the efficacy of Intuniv in the treatment of ADHD was established in 2 placebo-controlled trials in children and adolescents ages 6-17. In both studies, the primary outcome was the change from baseline to endpoint in mean ADHD Rating Scale-IV (ADHD-RS) scores. The ADHD-RS is a rating scale comprised of 18 clinician-rated items designed to assess the core symptoms of ADHD, which are stated in Intuniv's indication (see Background). While Intuniv showed statistically significant improvement in mean ADHD-RS score vs. placebo, this scale does **not** measure improvement in individual components of the ADHD-RS. Therefore, an improvement in the total ADHD-RS score does not necessarily correlate with a positive effect on individual components of the ADHD-RS.

Furthermore, the ADHD-RS does **not** measure behavioral problems such as "irritability," "arguing with adults," "temper outbursts," or "deliberately annoying others." These behavioral problems are not symptoms specific to ADHD, and we are not aware of substantial evidence or substantial clinical experience demonstrating an effect of Intuniv on these behavioral problems.

Moreover, the Conners' Parent and Teacher Rating Scales referenced in the Parent's Guide were **not** used to measure the efficacy of Intuniv in treating ADHD, and therefore claims that imply improvement in individual components of these scales are misleading.

Furthermore, page 7 of the Parents Guide includes the following claims (emphasis in original):

- "**Parents and teachers reported INTUNIV improved symptoms day and night**

  In a clinical study, parents of children taking INTUNIV reported . . . .
  - Symptom improvement with INTUNIV over a full day (as measured by parents) at 6 PM, 8 PM, and 6 AM the next morning when INTUNIV was taken in the morning"

The above claims misleadingly imply that Intuniv is efficacious for a full 24-hour day. We are not aware of substantial evidence or substantial clinical experience to support claims that Intuniv is efficacious for a full 24-hour day. If you have data to support these claims, please submit them to FDA for review.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The "Important Safety Information" section of the promotional materials states, "Do not give INTUNIV to your child if your child is allergic to guanfacine or anything else in INTUNIV." However, this section fails to communicate the important risk information from the WARNINGS AND PRECAUTIONS

section of the PI that Intuniv should also not be used concomitantly in patients taking other guanfacine-containing products (e.g., Tenex®).

In addition, promotional materials must include risk information in each specific part as necessary to qualify any safety or effectiveness claims made in that part (*Cf.* 21 CFR 202.1(e)(3)(i)). The 8-page Waiting Room Brochure presents numerous efficacy claims on the first 7 pages of the piece, but fails to convey **any** risk information specific to Intuniv on these pages. The only specific risk information is relegated to the back cover of the brochure. Similarly, the front side of the Brochure Holder presents effectiveness claims for Intuniv but fails to communicate any risk information associated with its use. Rather, the risk information for Intuniv is printed on the back side of the Brochure Holder where it is unlikely to draw the reader's attention. We note the statement, "Please see Important Safety Information on back panel [or cover] and accompanying Full Prescribing Information." on the front side of the Brochure Holder and Waiting Room Brochure; however this does not mitigate the misleading omission of risk information.

Moreover, the promotional materials further minimize the risks of Intuniv by failing to present risk information with a prominence and readability reasonably comparable with the presentation of claims relating to the effectiveness of the drug. Specifically, the promotional materials use large and colorful headers to highlight benefits of Intuniv therapy, including a prominent and compelling image of a child in a large monster suit, while the risk information appears in small font and in single-spaced paragraph format, and in many cases only appears at the end of each piece.

The overall effect of these presentations minimizes the risks associated with Intuniv and misleadingly suggests that Intuniv is safer than has been demonstrated.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The promotional materials include claims and presentations such as the following:

- **"Does your child's ADHD treatment get to what matters?**
  Reveal the kid within
  A difference the whole family can see" (Brochure Holder)

- "**A new medicine that treats a range of ADHD symptoms . . . .**
  Now there's a medicine that's different – one that has been shown to improve a range of symptoms of ADHD that can be disruptive at home and at school.
  Introducing INTUNIV" (Waiting Room Brochure, page 3)

As described above, the pieces also claim Intuniv has been studied across a range of symptoms, including behavioral problems such as arguing with adults, irritability, temper outbursts, and deliberately annoying others. These claims and presentations misleadingly imply that Intuniv is more efficacious than other ADHD medications in that it improves a range of symptoms that other ADHD medications do not treat, including the listed behavioral

symptoms. This implication is not supported by substantial evidence; we are not aware of any adequate and well-controlled head-to-head clinical trials demonstrating an advantage of Intuniv over other ADHD medications. Furthermore, as discussed in detail above, we are not aware of support for the implication that Intuniv improves individual behavioral problems in children. Therefore, these presentations are misleading.

Conclusion and Requested Action

For the reasons discussed above, the Brochure, Brochure Holder, and the Patient Starter Kit misbrand Intuniv in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (xviii) & (e)(7)(viii).

DDMAC requests that Shire immediately cease the dissemination of violative promotional materials for Intuniv such as those described above. Please submit a written response to this letter on or before July 6, 2010, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Intuniv that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS #18583 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Intuniv comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Susannah K. Hubert, MPH
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22037	ORIG-1	SHIRE DEVELOPMENT INC	INTUNIV: Guanfacine SR; tablet form

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSANNAH HUBERT
06/22/2010